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Malignant Lymphoma of the Kidney

YUTAKA YASUNAGA, MD,[1] YOSHIHIKO HOSHIDA, MD,[1] MICHIKO HASHIMOTO, MD,[1]
TSUNEHARU MIKI, MD,[2] AKIHIKO OKUYAMA, MD,[2] AND KATSUYUKI AOZASA, MD[1]*
[1]*Department of Pathology, Osaka University Medical School, Osaka, Japan*
[2]*Department of Urology, Osaka University Medical School, Osaka, Japan*

Background: Primary renal lymphoma (PRL) is a rare disease, making information including etiologic factors for PRL extremely limited.
Methods: Clinical and pathologic findings of PRL in Japan are presented and compared with those from Western countries. The presence of Epstein-Barr virus (EBV) genomes in the tumor was also evaluated. Eight cases of PRL were collected from a review of the ''Annual of the Pathological Autopsy Cases in Japan (1976–1992)''. These cases fullfilled the following criteria: (1) presence of renal mass without extrarenal lymphomatous involvement at admission and (2) absence of a leukemic blood picture. For histologic and immunohistochemical studies, 10% formalin-fixed and paraffin-embedded histologic specimens were used. Presence of Epstein-Barr virus (EBV) genome was examined by polymerase chain reaction (PCR) and in situ hybridization (ISH).
Results: There were five males and three females; age at admission ranged from 15 to 79 years (median 57 yr). Abdominal and/or flank pain were the most common presenting symptoms. No particular past history was present in any of the patients. Histologically, tumor cells in all cases showed a diffuse pattern of proliferation: large cell type in six cases, mixed cell type and small lymphocytic type in 1 each. Immunohistochemistry revealed B-cell nature of lymphoma cells in all cases. Neither PCR nor ISH showed the presence of EBV genome in any cases.
Conclusions: PRL is non-Hodgkin's lymphoma of predominantly large cell type with a B-cell immunophenotype. EBV etiology is unlikely in PRL.
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KEY WORDS: kidney; non-Hodgkin's lymphoma; Epstein-Barr virus; immunophenotype

INTRODUCTION

Renal involvement is a common finding in patients with advanced non-Hodgkin's lymphoma (NHL). A relatively lower frequency of 6.7% was reported by Weimar et al. [1] and much higher frequency of 37–47% by others [2,3]. Meanwhile, primary renal lymphoma (PRL) is an extremely rare disease, possibly due to the fact that the kidney is one of the extranodal organs usually not containing lymphoid tissue [3,4]. It accounts for 0.7% of all extranodal lymphomas in North America [5] and 0.1% of all malignant lymphomas in Japan [6]. Therefore, a large-scale study on PRL has rarely been done [7–12], and information regarding PRL remains extremely limited. Little is known about etiologic factors for PRL, although development of PRL in patients with acquired immunodeficiency syndrome has been reported [13].

Recent studies have shown the presence of Epstein-Barr virus (EBV) genomes in the tumor cells of B-cell lymphoma and much less frequently in T-cell lymphoma [14–20]. The presence of EBV genome could be demonstrated by the polymerase chain reaction (PCR) and in situ hybridization (ISH). In this report, clinical and pathologic findings in eight cases with PRL are presented

*Correspondence to: Katsuyuki Aozasa, M.D., Department of Pathology, Osaka University Medical School, 2-2 Yamada-oka, Suita, Osaka 565, Japan. e-mail: aozasa@molpath.med.osaka-u.ac.jp.
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and compared with those from Western countries. The presence of EBV in the tumor was also evaluated.

MATERIALS AND METHODS

Patients

Eight cases of PRL were collected from a review of the ''Annual of Pathological Autopsy Cases in Japan (1976–1992).'' These patients were admitted to hospitals during the period 1981–1991. Primary renal origin was defined as localization of lymphoma in the kidney, i.e., Stage I disease, when evaluated by the physical and roentgenographic examinations and/or the findings at surgery, which showed no evidence of disseminated disease. Histologic specimens obtained by surgery or autopsy were fixed in 10% formalin and routinely processed for paraffin embedding. Histologic sections, cut at 4 μm, were stained with hematoxylin and eosin and immunoperoxidase procedures (ABC method). All tumors were histologically classified according to the Working Formulation [21]. Adequate clinical and follow-up data were available in all but one case.

Immunohistochemical Studies

Histologic sections were treated with microwaves for 5 minutes in 10 mM citrate buffer (pH 6.0), thereafter incubated with mouse antihuman monoclonal antibodies Mx-panB(CD20)(Kyowa Medex, Tokyo, Japan, diluted at 1:50) MB-1(CD45RA), MT-1(CD43)(Bioscience, Emmenbrucke, Switzerland, diluted at 1:50), UCHL-1 and OPD4(CD45RO)(Dakopatts, Copenhagen, Denmark, diluted at 1:100). CD20 and CD45RA, which react with human B-lymphocytes, CD43 and CD45RO, which react with T lymphocytes.

DNA Extraction and Polymerase Chain Reaction

DNA was extracted from the paraffin-embedded tissue using chelating resin. The details of these procedures have been described [22]. Paraffin blocks without any samples were used for negative controls throughout the procedures. DNA extracted from the EBV positive Burkitt lymphoma cell line Raji (gift from Dr. H. Mizusawa, National Institute of Hygiene, Japan) was used for positive control of EBV DNA. Amplification was carried out using PCR. For the amplification of the β-globin gene, primers are designed to amplify 129 bp segment in exon 7–8 region (exon 7, 5′-CTTCTGACACAACTGTGTTCACTAGC-3′, and exon 8, 5′-TCACCACCAACTTCATCCACGTT CAC-3′) [23]. For the amplification of EBV genome, primers are designed to amplify 129 bp segment in the Bam HI-W region of EBV genome (5′-CCAGACAGCAGCCAATTGTC-3′, and 5′-GGTAGAAGACCCCCTCTTAC-3′) [24].

In Situ Hybridization

EBV RNA in situ hybridization was performed as previously described [18,25] with some modifications. Briefly, 30-base oligonucleotide probes, which were sense and antisense for a portion of the Epstein-Barr virus encoded RNA 1 (EBER-1) gene, a region of the EBV genome that is actively transcribed in latently infected cells [26], were synthesized using DNA synthesizer. As a positive control, the Raji cell line was used. As negative controls, the hybridizing mixture was employed with sense probe and antisense probe after RNAse treatment. All controls for each case were run in parallel in every experiment.

RESULTS

Clinical Findings

The clinical findings are summarized in Table 1. There were five males and three females with age at admission ranging 15–79 (median 57) years. Abdominal and/or flank pain was the most common presenting symptom. At presentation, B symptoms including fever and weight loss were found in two cases (1,4). One patient (Case 4) was suffering from hemorrhagic gastric ulcer and, therefore, could not receive the chemotherapy. No particular past histories were present in any of the patients. Roentgenographic examinations revealed the mass shadow in uni- (seven cases) or bilateral kidney (one case). Renal masses had a high density with mottled appearance in all cases but one by CT, which were suspicious of renal cell carcinoma. The angiography in two cases (2,5) demonstrated a hypovascular mass. In these two cases, intravenous pyelography revealed that the pelvicocalyceal structures were compressed by tumor, although the renal function was retained. In one case (3), location of abdominal masses at first could not be confined to either kidney or liver. However, subsequent CT and ultrasonographic examinations demonstrated the mass to be restricted to the kidney without extrarenal disease. In Case 8, the CT revealed involvement of the bilateral kidney, but there were no findings suggestive of spread of disease in the internal organs, including the lymph nodes, liver, and spleen. Serum level of lactate dehydrogenase (LDH) in this patient was slightly elevated at 321U. Laboratory data indicated presence of renal insufficiency in one patient (Case 2), anemia (Hb <8 g/dl) in three (5,7,8), and elevated serum level of LDH (>600 U) in seven (except for Case 8). Leukocytosis (WBC >10,000) was found in four patients (Cases 2,3,7,8) with no evidence of a leukemic blood picture. Microscopic hematuria and proteinuria were present at the time of the present illness in Case 6. Neither superficial lymphadenopathy nor hepatosplenomegaly was found at admission in any patient. The histologic diagnosis of malignant lymphoma was made at the open abdominal or echo-guided needle biopsy in four

TABLE I. Clinical Findings in Eight Patients With Malignant Lymphoma of the Kidney

Case	Sex	Age	Radiographic findings: Site of tumor[a]	Radiographic findings: Methods[b]	Presenting symptoms	Treatment	Chemotherapeutic agents[c]	Response[d]	Survival (mos)
1	M	62	Rt	US	Weight loss	Radiation + chemotherapy	CHOP + etoposide	PD	14
2	M	79	Rt	IVP, US, CT, MR, AG	Rt. flank pain	None	None	None	4
3	M	67	Rt	US, CT	Middle back pain	Chemotherapy	VEPA (7 cycles)	NR	2
4	M	71	Lt	CT	Lt.flank pain, fatigue	None	None	None	1
5	F	45	Lt	IVP, CT, AG	Fever	Chemotherapy	unknown	NR	1
6	M	76	Lt	CT	Microscopic hematuria and proteinuria	Lt nephrectomy + chemotherapy	CHOP (3 cycles)	NR	6
7	F	43	Lt	CT	Upper abdominal pain	None	None	None	1
8	F	15	Bil	CT	Bilateral abdominal mass	Chemotherapy	unknown	CR	20

[a]Lt: left, Rt: right.
[b]US: ultrasonography, IVP: intravenous pyelogram, CT: computed tomography, MR: magnetic resonance imaging, AG: angiography.
[c]CHOP: cyclophosphamide, adriamycin, vincristine, prednisone, VEPA: vincristine, cyclophosphamide, prednisone, adriamycin.
[d]PD: progressive disease, NR: no response, CR: complete remission, (−).

patients (Cases 1,3,5,8), at surgery in one (Case 6), and at autopsy in three (Cases 2,4,7).

One patient received radical nephrectomy followed by the adjuvant chemotherapy. Three patients received chemotherapy alone, and one received radiotherapy and chemotherapy. In the remaining three patients, neither nephrectomy nor adjuvant chemotherapy could be carried out due to renal failure (Case 2), asthma attack (Case 4), or respiratory dysfunction (Case 7). Follow-up data showed that all patients died of tumor within 2 years after the surgery; the median survival was 6 months.

Pathologic and Immunohistologic Findings

At surgery in Case 6, the tumor was confined to the medulla of the left kidney. In the remaining seven cases, direct observation of the abdominal cavity was possible only at autopsy: renal masses were found confined to the kidney in one case and invading the perinephric tissues, including retroperitoneum, ipsilateral adrenal gland, duodenum, and ureter in six patients. Autopsy revealed a dissemination of tumors in the liver in three cases, diaphragma in two, pericardium in one, rectum in one, and meninx at the base of brain in one. Measurement of the renal tumor revealed the smallest to be 14 × 19 cm and the largest to be 30 × 30 cm. At cut surface, the yellowish-white tumor with varying degrees of hemorrhage and necrosis occupied the renal parenchyma. Tumor cells showed a diffuse pattern of proliferation in the parenchyma and occasionally invaded into the perinephric adipose tissue. All were NHL: large cell type in six cases (75%), mixed cell type in one, and small lymphocytic type in one. Mitotic figures ranged from 3–63 (mean 25) per 10 high power fields. Histologic findings suggesting the presence of chronic inflammation could not be found except for the marked arteriosclerotic nephrosclerosis in one (Case 2). Immunohistochemistry revealed that all were B-cell lymphoma with the constant positive reactivity for CD20. Large cells in one case (Case 7) showed a positive reactivity for OPD4, a marker for T-lymphocytes. However, OPD4 is known to frequently react with B-lymphocytes.

EBV Genome

Neither the PCR nor ISH method showed the presence of EBV genome in any of the present cases.

DISCUSSION

It has been a controversial issue whether PRL is a definite entity or not. Because renal tissue usually contains no lymphoid tissues, some investigators doubted the presence of PRL [4,7]. Others postulated that the lymphatics in the renal capsule might be the source of lymphoma, which subsequently invade into the renal parenchyma [27]. In other extranodal organs, lymphoid tissues formed by the chronic inflammation are regarded as the sources for development of malignant lymphoma [5], i.e., Hashimoto's thyroiditis for thyroid lymphoma [28], follicular gastritis for gastric lymphoma [29], chronic sialadenitis for salivary gland lymphoma [30], and so on. Recent reports with adequate roentgenographic information supported the presence of primary lymphoma of the kidney [11], although the presence of lymphoid tissue in or near the lymphoma was not mentioned. As described below, all of the present cases fulfilled the criteria for the diagnosis of PRL. However, we could not confirm the presence of lymphoid tissue. Review of the clinical histories in the present cases did not reveal any particular past history, including chronic inflammatory diseases.

Use of modern roentgenographic techniques is essential for determination of the primary nature of renal lymphoma. We could collect PRL cases fulfilling the following criteria: (1) presence of renal mass, (2) no evidence of extrarenal lymphomatous involvement in the visceral organs or lymphnodes at first admission, (3) absence of a leukemic blood picture together with no evidence of myelosuppression. The present roentgenographic findings revealed that all of our cases had mass lesions confined to the kidney. In one case, a huge mass replaced the right kidney and directly invaded the liver and retroperitoneal cavity.

A slight male preponderance was common in our as well as previous reports on PRL [11], although females predominated in the cases reported by Okuno et al. [12]. The PRL usually affects adults [11,12]. All but one of the present cases were adults with age ranging from 43 to 79 years with a mean of 63 years. One patient was a 15-year-old girl with a diffuse immunoblastic lymphoma. Renal lymphoma is much less common in children than in adults, and when it occurs, it is usually small noncleaved cell type (Burkitt's) or less frequently, lymphoblastic lymphoma [11].

Flank pain was the most common presenting symptom in patients with PRL in the previous reports [11,12] and in the present patients. Other symptoms included abdominal mass, hematuria, and systemic symptoms such as fever, weight loss, and fatigue. Renal insufficiency developed during the course in one of our patients (Case 2) with unilateral renal involvement. In the previous reports, parenchymal involvements of the bilateral kidneys seemed to be associated with renal insufficiency [9,11,31,32]. One patient was suffering from hemorrhagic gastric ulcer; therefore, chemotherapy was not possible. All these factors might worsen the prognosis of the current patients in spite of localized disease. All of the current cases died within 2 years after the start of treatment. Poor prognosis of patients with PRL was also reported from Spain [10] and the U.S. [12], i.e., median time of survival was 16 months and 8 months, respectively. Meanwhile some investigators reported a rather favorable prognosis of patients with PRL; mean survival was approximately 3 years in one series [8] and more than half of patients survived >2 years in another [11]. It seems that early detection of disease and systemic adjuvant therapy may contribute to the improvement of the prognosis.

All of the present patients had NHL of diffuse type with the large cell type being the most common. This is in agreement with the previously reported findings on the PRL [9,11–13]. One (9%) of 11 cases reported by Ferry et al. [11], but none of the present eight cases had follicular lymphoma, showing this type to be unusual in PRL. Immunohistochemistry revealed that all of the present cases had B-cell lymphoma, which is consistent with previous reports [9,11–13,31,32]. The present study together with the previous reports showed that the NHL arising in the urologic organs, including kidney, testis [33], urinary bladder [34], and urethra [35], were exclusively B-cell lymphoma.

Recently, evidence suggesting an etiological role of EBV in the development of B-cell lymphoproliferative diseases has been accumulating [14–16]. The majority of acquired immunodeficiency syndrome-related [36] and organ transplant-related lymphomas [15,17], had diffuse large cell or small noncleaved cell morphologies are well known to be associated with EBV. All but two of our cases had large cell lymphoma, although the PCR and ISH studies failed to detect EBV genome in the tumor cells, suggesting that the PRL is not an EBV-associated tumor.

In conclusion, PRL is non-Hodgkin's lymphoma of predominantly large cell type and has the B-cell phenotype with poor prognosis. It is unlikely that EBV plays a role in the development of renal lympohoma and etiological factors remain unknown.

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